Postpartum haemorrhage – an international perspective

Svensk förening för Obstetrik och Gynekologi, Tallberg
14th April 2015

P J Steer
Emeritus Professor of Obstetrics

Academic Department of Obstetrics and Gynaecology
Chelsea and Westminster Hospital
PPH – a global perspective

• Part one
  – epidemiology and pharmacology

• Part two
  – The surgical aspects
Part one - epidemiology and pharmacology

• Who is most likely to get a PPH?
• Are we giving too much blood?
• Which components of the ‘active management of the third stage’ are really necessary?
• Which pharmacological agents should we use to reduce bleeding?
• What are their side effects?
The global problem

• Global maternal mortality 289,000 PA
• Mostly preventable
• 27% due to severe bleeding
• 200 deaths per day due to haemorrhage

WHO fact sheet number 348, Updated May 2014
http://www.who.int/mediacentre/factsheets/fs348/en/
Most deaths due to PPH are preventable

Relative territory size shows the proportion of maternal deaths during or within 6 weeks of pregnancy

http://www.worldmapper.org

Major global causes of maternal death
percent of deaths due to:

Contributors to maternal death from PPH

- poverty
- distance
- lack of information
- inadequate services
- cultural practices

Causes of maternal death in the UK
Deaths per 100,000 maternities

- Hypertension
- Sepsis
- Thrombosis
- Cardiac
- Haemorrhage
Number of maternal deaths 2006-8

- Cardiac: 53
- Sepsis: 26
- Pre-eclampsia/eclampsia: 19
- Thrombosis: 18
- Haemorrhage: 9

Number of maternal deaths 2006-8
Number of maternal deaths 2009-11

- Cardiac: 51
- Thrombosis: 30
- Sepsis: 14
- Haemorrhage: 14
- Pre-eclampsia/eclampsia: 10
Definition of PPH

- ≥500 ml
- ≥1000 ml
- Blood loss is difficult to measure
- Hb drop ?
- Blood transfusion
NorthWest Thames Obstetric Database 1988-2000

- 17 maternity units
- On-line validation of data entry
- 501,823 births with birthweight
TRANSFUSION BY MODE OF DELIVERY

% transfused

- Spontaneous
- Assisted breech
- Ventouse
- Elective caesarean
- Breech extraction
- Lift out forceps
- Other forceps
- Emergency caesarean
- Rotational forceps
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>White European</td>
<td>362,630</td>
</tr>
<tr>
<td>Black African</td>
<td>17,095</td>
</tr>
<tr>
<td>Black Caribbean</td>
<td>14,557</td>
</tr>
<tr>
<td>South Asian</td>
<td>66,409</td>
</tr>
</tbody>
</table>
Spontaneous deliveries only

% Transfused postnatally

Mothers racial group

- White European
- Black African
- Black Caribbean
- South Asian
- Oriental
- Mediterranean
- Any other ethnic group
Are we giving too much blood?

- Risk of blood transfusions:
  - Overloading the circulation
  - Transfusion reactions
  - Infection
    - Hepatitis C
    - HIV
    - Prion disease
- Giving too much can be as bad as giving too little
How much blood should we give?

- To lose one unit (500ml) at delivery is probably ‘normal’ and physiologically neutral given the plasma volume expansion of pregnancy.
- A healthy person can easily make up one unit of additional loss.
- ? replace estimated blood loss minus 1000ml.
If you need to give blood, give two units - ‘to be on the safe side’
Top 5 overused interventions:

- Antibiotics for viral URTI
- **Blood transfusion**
- Tympanostomy tubes (grommets)
- Early term delivery
- Percutaneous cardiac stenting
While blood transfusions can be life-saving, they also carry risks that range from mild complications to death.

Variation in clinical transfusion practices results in waste of a limited resource when unnecessary transfusions are given.
All the variability shows "there is both excessive and inappropriate use of blood transfusions in the U.S.," advisers to Health and Human Services Secretary Kathleen Sebelius concluded earlier this month. "Improvements in rational use of blood have lagged."
The rule “less is more” doesn’t usually apply to matters of life and death, but researchers from Rutgers University argue there may be a case for it. Smaller infusions not only reduce the immediate risk of death from disease and other illnesses, but keep more people alive over the long-term. Three-year survival rates showed marked spikes among those who received less blood.

“I think it is very reassuring that we have found that using less blood is okay not just from a short-term perspective, but also a long-term perspective,” said Dr. Jeffrey Carson, lead author and chief of the Division of Internal Medicine at Rutgers Robert Wood Johnson Medical School, in a statement.
EDITORIAL

Transfusion Threshold of 7 g per Deciliter — The New Normal

Paul C. Hébert, M.D., and Jeffrey L. Carson, M.D.


Photo: John Emerson
Jeffrey Carson says it is clearer than ever that smaller transfusions are better for many patients than larger ones.
Controlling postpartum haemorrhage

- Prophylaxis
- Treatment
Prophylaxis by active management of the third stage

- early cord clamping
- controlled cord traction to deliver the placenta
- prophylactic uterotonic
Delayed cord clamping may be preferable

- A more liberal approach to delaying clamping of the umbilical cord in healthy term infants appears to be warranted.

- Growing evidence that delayed cord clamping increases early haemoglobin concentrations and iron stores in infants.

- Delayed cord clamping is likely to be beneficial as long as access to treatment for jaundice requiring phototherapy is available.

Hospitals warned to delay cutting umbilical cords after birth

Cochrane Library research finds newborns receive more iron if umbilical cord is left for several minutes before being clamped

Denis Campbell, health correspondent

Thursday 11 July 2013 00.01 BST

The NHS is now facing calls to rethink a policy that has been standard for about 50 years regarding when umbilical cords are cut. Photograph: Stephen Chiang

Hospitals are under pressure to stop clamping newborn babies' umbilical cords after new research found that their health improves if the cord is left to pulse for several minutes.
Active management of the third stage

• Seven studies (8247 women), 6 in high-income countries
• Active management reduced the average risk of maternal primary haemorrhage (more than 1000 ml)
• Risk ratio (RR) 0.34, 95% confidence interval (CI) 0.14 to 0.87, three studies, 4636 women
• Hypertension and interference with placental transfusion might be avoided by using modifications e.g. omitting ergot and deferring cord clamping

Active management of the third stage – PPH rates

- Prendiville 1988 – 5.9% vs 18.0%
- Begley 1990 - 2% vs 8%
- Rogers 1998 – 6.8% vs 16.5%

Uterotonics

- Syntocinon
- Ergometrine
- Syntometrine
- Misoprostol (oral, vaginal, rectal)
- 15-methyl prostaglandin F2 alpha (carboprost/hemabate)
- Carbetocin
HIPPOCRATES
5C BCE

Oxytocin release from the posterior pituitary

Sir Henry Dale

- Cat model, balloon catheters in bladder, bowel and uterus
- Injected posterior pituitary extract
- Noticed that it made the uterus contract

H. H. Dale.
On some physiological actions of ergot.
Sir William Blair-Bell

- Used extract of posterior pituitary to control postpartum haemorrhage

W. Blair Bell.
Oxytocin synthesised 1956 by Vincent du Vigneaud

- 1954 Journal of the American Chemical Society 76 (12): 3115–3118
- Awarded the Nobel Prize
ERGOT

- Symptoms of ergotism first clearly described in the middle ages (from 857 AD) – known as ‘Saint Anthony’s fire’
- Use in labour from 16th century
- 1906 Barger and Carr isolated ergotoxine
- 1918 Stoll discovered ergotamine
- 1935 Chassar Moir showed effect in puerperal uterus
- With H Dudley Ward FRS isolated ergometrine

Chassar Moir J, J Can Med Ass 1955, 72, 727-734
Ergotoxine 0.5 mg. by intramuscular injection.

Ergotamine 0.5 mg. by intramuscular injection.

Fig. 6.—Tracing from the human postpartum uterus showing the effect of ergotoxine and of ergotamine after intramuscular injection. Note the long delay in the onset of effect (20 minutes or more); when given by mouth the delay was in excess of two hours.
Fig. 7.—The effect of liquid extract of ergot (B.P. 1914) given by mouth to a puerperal woman. Note the suddenness of the action (4½ minutes in this case).
Misoprostol

• Analogue of prostaglandin E1
• Registered as ‘Cytotec’ from 1985
• Licensed for treatment of peptic ulcers
• Discovered by chance to ‘bring on periods’
• By 1990, used in high proportion of clandestine abortions in Brazil

Weeks A and Faundes, IAJGO, 2007, 99, S156-159
Misoprostol

• Used in cases of intrauterine death
• Used to induce labour
• Used to reduce PPH in areas without effective cold storage
• In 78 RCTs including 59,216 women, NOT found to reduce maternal deaths or major morbidity

Weeks A and Faundes, IAJGO, 2007, 99, S156-159
Other agents to reduce bleeding

• Tranexamic acid
• Recombinant factor VIII
• Fibrinogen
Tranexamic Acid
antifibrinolytic agent

- Antifibrinolytic agent that prevents clot breakdown by blocking lysine sites on plasminogen molecules
- Can be used when there is a RISK of haemorrhage
- Inhibits fibrinolysis with no effect on clotting parameters
- Use in trauma patients within 1 hour reduces risk of death by 32% (RR 0.68 95% CI 0.57-0.82)

Tranexamic acid

- WHO now sponsoring double-blinded RCT with 15,000 women to determine effect on death and other morbidities

http://www.thewomantrial.lshtm.ac.uk/
Recombinant Factor VIIa

- Review of published cases of amniotic fluid embolism
- Sixteen rVIIa cases and 28 cohorts were identified
- Risk ratio 2.2, 95% CI 1.4-3.7 for death or permanent disability vs. full recovery
- Recombinant factor VIIa cases had significantly worse outcomes than cohorts who did not receive rVIIa.
- It is recommended that rVIIa be used in AFE patients only when the hemorrhage cannot be stopped by massive blood component replacement

Leighton BL et al, Anesthesiology. 2011,115:1201-8
Massive Blood Transfusion protocol

Fibrinogen concentrate to correct hypofibrinogenaemia


Courtesy Prof Arulkumaran
Dangers in routine use of uterotonic agents

- Syntometrine is routinely used to reduce the risk of postpartum haemorrhage by 40%
- Contains ergometrine 0.5mg and syntocinon 5IU

http://www.medicines.org.uk/emc/medicine/135/SPC/Syntometrine+Ampoules/
**RISK OF HYPERTENSION WITH ERGOMETRINE**

**Analysis 1.8. Comparison 1 Ergot alkaloids and no uterotonic agents, Outcome 8 Elevation of blood pressure.**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Ergot alkaloids n/N</th>
<th>Placebo or no agents n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Random,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGinty 1956</td>
<td>26/100</td>
<td>6/50</td>
<td></td>
<td>30.9 %</td>
<td>2.17 [0.95, 4.92]</td>
</tr>
<tr>
<td>Howard 1964</td>
<td>238/505</td>
<td>155/475</td>
<td></td>
<td>40.3 %</td>
<td>1.44 [1.23, 1.69]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>1310</strong></td>
<td><strong>1249</strong></td>
<td></td>
<td><strong>100.0 %</strong></td>
<td><strong>2.60 [1.03, 6.57]</strong></td>
</tr>
</tbody>
</table>

Total events: 299 (Ergot alkaloids), 166 (Placebo or no agents)
Heterogeneity: Tau² = 0.55; Chi² = 12.60, df = 2 (P = 0.002); I² = 84%
Test for overall effect: Z = 2.02 (P = 0.043)

---

Liabsuethrakul T, Choobun T, Peeyananjarassri K, Islam QM.
Prophylactic use of ergot alkaloids in the third stage of labour.
Cochrane Database of Systematic Reviews 2007,
Ergometrine causes coronary artery spasm

- Canine model
- both 5-HT and ergometrine consistently induced contraction of coronary arteries

Ergometrine and myocardial infarction


2. Sutaria N, O'Toole L, Northridge D. Postpartum acute MI following routine ergometrine administration treated successfully by primary PTCA. *Heart* 2000; 83(1):97-98.


Don’t give ergometrine to women with:

- Hypertension
- Cardiac disease
- Low risk of PPH
  - Avoids risk of nausea and headache
PREVENTION AND MANAGEMENT OF POSTPARTUM HAEMORRHAGE

Syntometrine (© Alliance) may be used in the absence of hypertension (for instance, antenatal low haemoglobin) as it reduces the risk of minor PPH (500-1000 ml) but increases vomiting.

For women without risk factors for PPH delivering vaginally, oxytocin (5 iu or 10 iu by intramuscular injection) is the agent of choice for prophylaxis in the third stage of labour.
**Figure 9.1** Arterial pressure in a patient during caesarean section under spinal anaesthesia; note the decrease in blood pressure after five units of Syntocinon® on two occasions (courtesy of TH Clutton-Brock and GM Cooper)
CARDIOVASCULAR EFFECTS OF SYNTOCINON

- Vasodilatation in the subcutaneous vessels
- Vasoconstriction in the splanchnic bed and coronary arteries
- Direct effect on cardiac receptors increases heart rate
- Net effects:
  - Hypotension
  - Tachycardia
  - Myocardial ischaemia

2. Jonsson M et al, BJOG. 2010;117(1):76-83
CARDIOVASCULAR EFFECTS OF SYNTOCINON

- Administration of 5 IU bolus reduces mean arterial pressure by an average of 27mm Hg\(^1\)
- Uterotonic efficacy of 2 IU similar but fewer haemodynamic side-effects\(^2\)
- Bolus of 0.35 IU plus continuing low dose infusion (40 mU/min) may be optimal\(^3\)

For women delivering by caesarean section, oxytocin (5 iu by slow intravenous injection) should be used to encourage contraction of the uterus and to decrease blood loss.

A bolus dose of oxytocin may possibly be inappropriate in some women, such as those with major cardiovascular disorders, suggesting that a low-dose infusion might be a safer alternative.
Misoprostol and pyrexia

- 78 studies (59,216 women)
- No difference in maternal mortality, even against placebo
- All 11 deaths with misoprostol were in studies of >=600 µg
- Pyrexia >38°C 10.8% vs 2.3%
- “Given that misoprostol is used prophylactically in very large numbers of healthy women, the greatest emphasis should be placed on limiting adverse effects”

Summary

• PPH is still a major global killer
• Management in the developed world is effective
• Mode of delivery is the major risk factor
• We should not give blood ‘just in case’
• Oxytocin is the best uterotonic but misoprostol may be useful if refrigeration is not available
• All uterotonicics have important side-effects
An early warning scoring system for detecting developing critical illness.

Clin Intensive Care 1997;8:100

Morgan RJM, Williams F, Wright MM

Blackpool, Great Yarmouth, UK
MEWS (modified early warning score), Rule of 30, Shock Index

- 30% blood loss > moderate shock
- Pulse rate – increase > 30 bpm
- Respiratory rate > 30/min
- Systolic BP – drop by 30 mm Hg
- Urinary output < 30 ml/hour
- Haematocrit drop > 30% & to be kept at an absolute value of > 30

- Shock Index = Pulse rate / Systolic BP – Change by 30%
  Normal = 0.5 to 0.7 : >0.9 indicates state of shock that needs urgent resuscitation
Does MEWS work?

- Prospective quasi-experimental trial in the Academic Medical Center in Amsterdam included three medical and three surgical wards
- A group of 47 trained and 48 non-trained nurses were presented with a case of a deteriorating patient, and subsequent assessment and actions regarding the patient case were measured.
- Respiratory rate was measured twice as frequently (53% trained versus 25% non-trained, p=0.025). No differences were found in the measurement of other vital parameters.
- Despite rigorously implementing MEWS/SBAR* methodology, these tools were rarely used.

*Situation-Background-Assessment-Recommendation
Does MEWS work?
Patel MS et al, Injury, 2011 Epub ahead of print

• The MEWS system was implemented in all trauma and orthopaedic wards at the Leicester Royal Infirmary in the summer of 2005

• In view of the apparent lack of clinical effectiveness of the MEWS/outreach partnership, the cost effectiveness of this initiative needs to be questioned
MEWS and intrauterine infection

- MEWS criteria do not identify accurately patients who are at risk for intensive care unit transfer, sepsis, or death among pregnant women with intrauterine infection and should not be used in an obstetric setting.